REMARKS

This document is submitted in response to the Office Action dated June 10, 2010. Applicants have presently amended claims 14, 22 and 23. The amendments to claim 14 find support in the Specification on page 4, lines 5-15; Example 3, beginning on page 14 at line 10 and Table I. The amendments to claim 23 find support in the Specification e.g. on page 11, lines 29-38. Other amendments were made to improve clarity, and/or to correct antecedent basis. Applicant believes that no new matter has been added.

Upon entry of the proposed amendments, claims 14-26 will be pending and under examination. Applicants respectfully request that the Examiner reconsider this application in view of the following remarks.

A. Response to rejections under 35 USC §103: Chaudhary in view of Wennemuth

In the present Action, pending claims 14-15 and 17-20 are rejected under 35 U.S.C. 103(a) as unpatentable over Chaudhary et al. (2001) ("Chaudhary") in view of Wennemuth et al. (2003) (which includes the Correction to FIGURE 9 that was published on June 30, 2003) ("Wennemuth"). Specifically, the Action indicates that Chaudhary discloses all aspects of the present claims with the exception of achieving a contraceptive effect comprising a PMCA4 isoform inhibitor (or a method for diagnosing infertility in a human male), and that Wennemuth fills in this gap by teaching the skilled person that the PMCA pump is involved in the fertilization of human eggs by sperm, and thus a target for PMCA inhibition, such that the skilled person could arrive at the presently claimed invention with a reasonable expectation of success (Office Action, pages 10-11). Applicants respectfully traverse this rejection for the reasons provided below:

I.

Claim 14, as amended, is drawn to a method of achieving a contraceptive effect that comprises administering an inhibitor directed against a plasma membrane calcium ATPase 4 (PMCA4) isoform, which is expressed in a sperm cell. Administration of said inhibitor is, as

disclosed in the application, performed to thereby inhibit sperm mobility such that fertilization of an egg cannot take place, that is, to achieve a contraceptive effect.

The present amendments to claim 14 make clear that the inhibitor acts on PMCA4 pumps that are present within the sperm cell to elicit the stated contraceptive result. Moreover, this claim now states that the desired inhibition is such that the sperm cells are rendered non-motile to the extent that sperm penetration of the egg membrane to cause fertilization is therefore not possible.

II-a.

Although the Chaudhary disclosure, cited presently as the primary reference, has been discussed at length during the prosecution of the instant application, Applicant would like to respectfully emphasize, in addition to those arguments already on record, that Chaudhary fails to supply the skilled person with key technical teachings necessary to practice the present invention. Applicant further wishes to note that these deficiencies are not remedied with the further consideration of Wennemuth.

To support use of the Chaudhary in the present rejection, the Examiner alleges that this disclosure teaches that "PMCA4 only differed from PMCA1b by one residue" (Office Action, page 3) and that "Caloxin 2A1 was able to inhibit PMCA1b but also produced a complete inhibition of plasma membrane ATPase in erythrocytes that expresses mainly PMCA4" (Office Action, page 4) to support a conclusion that "Chaudhary suggests that Caloxin 2A1 would also inhibit **all of the PMCA isoforms**"(Office Action, page 4).

Applicant respectfully notes that there appear to be quite a few logical leaps that the skilled person must make in order to firmly conclude that Caloxin 2A1 would factually inhibit the PMCA4 isoform in a sperm cell, including: "PMCA1b differs solely by one residue substitution and thus should not prevent caloxin from binding PMCA4" (Office Action pages 4 and 9) and that "Caloxin 2A1 was able to produce a complete inhibition (i.e. a high degree of inhibition) which would suggest inhibition of PMCA4"..."thereby suggesting that caloxin is also

effective against PMCA4" (Office Action, page 4; ***citing C1029***, left col., last paragraph). Applicant notes that the citation from C1029, ***in full,*** states "This suggests that caloxin 2A1 would inhibit all the PMCA isoforms, **but it remains to be established"**—thus telling the skilled person that further research is required to confirm the author's hypothesis. This statement undoubtedly negates the conclusion that a blanket inhibition of all PMCA isoforms by Caloxin2A1 is in fact obvious: and that this link has not simply been sufficiently established to support a finding of obviousness using the Chaudhary disclosure according to this rationale.

Importantly, Chaudhary's own experiments tell us that Caloxin 2A1 inhibition of PMCA in different cell types is **inconsistent**:

> ...caloxin 2A1 inhibits the Ca^{2+}-Mg^{2+}-ATPase in the erythrocyte ghosts by 78 +/- 4%, but it has **no effect** on Mg^{2+}-ATPase or Na^{+}-K^{+}-ATPase in the ghosts or **Ca^{2+}-Mg^{2+}-ATPase in the skeletal muscle sarcoplasmic reticulum** (FIG. 1B). **Thus caloxin 2A1 inhibits Ca^{2+}-Mg^{2+}-ATPase selectively**." (C1028, right-hand col.; emphasis added)

Accordingly, the skilled person reading the above passage must conclude that the use of Caloxin 2A1 to inhibit a particular PMCA isoform in a particular tissue cell type has to be empirically determined in order to confirm the existence of an inhibitory effect in that cell. In view of this passage, the assumption that Caloxin 2A1 behaves similarly in all cell types, in particular that Caloxin 2A1 would necessarily inhibit PMCA4 pumps in a sperm cell (which was not tested by Chaudhary), is simply not tenable.

In order to satisfy the deficiencies of the Chaudhary, the Examiner turns to Wennemuth, which is stated to demonstrate "the presence of PMCA pumps in sperm cells" (Office Action, page 5) and that "calcium is considered a regulator of sperm motility" and otherwise participates in the fertilization event (Office Action, page 10), which is offered to support a conclusion that "given that sperm cells express PMCA ATPase pumps and given the teaching of Chaudhary, one of ordinary skill in the art would have indeed found it obvious to try Caloxin 2A1 to inhibit PMCA in sperm cells" and that "inhibition of PMCA would necessarily result in a contraceptive effect" (Office Action, page 5 and pages 10-11).

Even if a skilled person were to use the Chaudhary methods, which Applicants do not concede, the Wennemuth disclosure is not sufficient to remedy the deficiencies of Chaudhary when considering the purpose and features of the subject-matter required by claim 14, as the methods differ in several meaningful respects.

Applicant wishes to maintain all arguments currently of record, in addition to emphasizing the following points:

In the Action (page 5), the Examiner rejects Applicant's "synergy argument" (where Wennemuth teaches that PMCA and NCX Ca^{2+} pumps act in synergy such that Ca^{2+} clearance cannot be attributed exclusively to PMCA channels) based on the idea that the claims as written "do not exclude the presence of additional Ca^{2+} pumps". Applicants consider that such an exclusion would go beyond the scope of the invention, which is clearly concerned with characterizing the behavior of PMCA4 pumps and inhibitors acting thereon within a sperm cell—in particular the resulting inhibition of sperm mobility leading to a contraceptive effect.

Moreover, the synergy argument is important since the skilled person is unable to distinguish the role of the PMCA and NCX Ca^{2+} pumps for Ca^{2+} clearance within the sperm cell, in particular since Wennemuth states that the NCX Ca^{2+} pumps have: a ***higher capacity*** for exporting Ca^{2+} compared to PMCA pumps (page 116, left-hand col.); that "***significant*** NCX is

present" in sperm cells (page 119, right-hand col. and FIG. 4); that "two plasma-membrane Ca^{2+} transporters dominate rapid Ca^{2+} clearance (i.e. PMCA & NCX, page 118, right-hand col.); and that "[t]ogether, the PMCA and the NCX are ***dominant routes*** of Ca^{2+} clearance in sperm"(page 120, bottom right-hand col.). In addition, to further complicate matters, the authors admit that the relative action of these two pumps may be ***pH dependent*** (page 120, from left-hand col., 2nd para to right-hand col. 1st para). Therefore, the skilled person seeking to reliably prevent contraception by inhibiting PMCA4 pumps in a sperm cell could not reasonably expect that the application of a PMCA inhibitor alone could in fact completely prevent a fertility event as presently claimed, given the dominant presence, capacity, and possible pH-dependency of the co-acting NCX pumps.

The Examiner also states that "Wennemuth was provided to demonstrate the role of Ca^{2+} in regulating sperm motility, sperm capacitation and involvement in acrosome reaction" (Office Action, page 6, 10), and that the Ca^{2+} is regulated by PMCA4 pumps (and thus inhibited by Caloxin 2A1 based on the Examiner's interpretation of Chaudhary). However, Applicant respectfully notes that this rejection is untenable since Wennemuth could only demonstrate immunohistological mapping of the PMCA pumps to the **tail portion** ("flagellum") of the mouse sperm, **but the "midpiece and head" (*acrosomal*) portions** of the sperm cell **were unlabeled** (page 121, left-hand col, 3rd para. PMCA antibody panspecific clone 5F10 was used: page 116, right-hand col: "Materials").

Conversely, as noted below, the present inventors in fact demonstrated clear immunological mapping using a purified *PMCA4* isoform to the **tail *and* acrosomal portions** of both murine and human sperm cells (FIG. 2). Given the stated importance of at least the acrosomal portion of the sperm (and Ca^{2+}) in fertilization, and that Wennemuth teaches that PMCA pumps could not be localized there, the skilled person would not reasonably expect that a purposeful inhibition of PMCA4 would reliably lead to a contraceptive effect as claimed.

Consequently, considering the Wennemuth results, the skilled person cannot conclude that the application of Caloxin 2A1 according to Chaudhary would be sufficient to prevent

fertilization in the manner required by instant claim 14, in particular since: (i) Chaudhary teaches that a tissue-specific effect for Caloxin 2A1 (and did not test sperm cells); and (ii) the specific and direct impact of PMCA-modulated calcium clearance on actual sperm motility and/or on acrosomal function were not demonstrated or described in Wennemuth. Applicant notes that Examiner seems to believe otherwise with the statement: "Because binding of caloxin 2A1 leads to reduction in sperm motility..." (Office Action, bottom of page 6), and respectfully invites the Examiner to provide evidentiary support for this conclusion from the cited references, especially since this conclusion forms the basis of the present rejection.

II-c.

A plain reading of the instant specification clearly demonstrates that **creativity, effort, and testing** were required to engineer and confirm the feasibility of the application of PMCA4 inhibitors to sperm cells bearing PMCA4 pumps in the claimed methods such that a contraceptive effect could, in fact, be provided with advantages over known techniques. Applicant considers that these investigations were necessarily conducted to substantiate the usefulness of these inhibitors as described and claimed, and are the product of ingenuity and not a product of routine measures.

Specifically, the inventors have empirically demonstrated for the first time the particular expression and localization (i.e. in the **tail and the acrosome**) profiles of PMCA4 in *both* mouse and human sperm. See Example 2 on page 13 beginning on line 25 and accompanying FIG. 1. Importantly, the inventors empirically demonstrated for the first time that sperm mobility in PMCA4-"knock-out" mice was deficient to such an extent that fertilization of an egg cell could not take place, thus rendering these mammals incapable of reproduction. See the experiments performed in Example 1, e.g. on page 13, lines 9-24 and in FIG. 2 with accompanying description on page 3, lines 18-29.

Furthermore, the inventors also recognized that the mobility of human sperm could be *purposefully restricted* through the specific inhibition of PMCA4 to thereby create a

contraceptive effect by preventing a fertilization event (Specification on page 5, lines 10-21), which they empirically demonstrated in Example 3, wherein up to 97% non-motile sperm were observed using the exemplary PMCA4 inhibitor (see Table I). To further confirm this observed effect, additional experiments were conducted using an alternative evaluation method (the CASA System 4.2) as described (page 15, line 15 to page 16, line 9).

Accordingly, Applicant believes that the significance of PMCA4 on sperm function, namely that PMCA4 inhibition could be effectively targeted for an anti-contraceptive purpose had, before the date of the instant invention, never been taught nor suggested. For instance, a human male subject can be administered with the described PMCA4 inhibitors to elicit a contraceptive effect, in the manner described by the instant invention, with the advantage that potentially serious side-effects using known contraceptive techniques are eliminated, including permanent infertility and feminization of the male body. See, e.g. page 9, lines 29-34.

II-d.

In view of the above discussion, it is unclear to Applicant why the skilled person, seeking to inhibit sperm mobility such that fertilization of an egg is prevented through the specific use of a inhibitor on PMCA4 expressed in sperm cells, would be motivated to begin with, and modify, a disclosure whose teachings as a whole do not *clearly* demonstrate that one such PMCA inhibitor (Caloxin 2A1) consistently inhibits PMCA in all cell types (considering the guidance in e.g. MPEP 2141.02). One skilled in the art reading Chaudhary would immediately understand that PMCA could be inhibited in some but not all cell types. Moreover, even if Caloxin 2A1 was shown to inhibit PMCA in a given cell such as a sperm cell, the skilled person cannot reasonably expect that Caloxin 2A1 would inhibit all PMCA isoforms present in that cell, according to Chaudhary's own admission (page C1029, bottom left-hand col.). Consequently, Chaudhary's complete omission of confirmed PMCA4 localization and testing in sperm cells coupled with the uncertainty of Caloxin 2A1 action on individual PMCA isoforms and cell-types should be construed as a clear indicia of the nonobviousness of the present invention.

Thus, a skilled person in the art seeking to prevent a fertilization event using an inhibitor against PMCA4 pumps expressed in a sperm cell, would have neither a motivation nor a reasonable expectation of success to use or modify the Chaudhary teachings. To the contrary, and to emphasize, as Chaudhary teaches that Caloxin 2A1 does not predictably inhibit PMCA in all cell types, it teaches one skilled in the art away from the method of claim 14 (and associated dependent claims).

For the reasons and facts set forth above, in particular since the cited documents did not recognize and could not predict that a method having the features recited in claim 14 could reliably provide a dependable contraceptive method that avoids undesirable side-effects associated with known techniques, Applicant submits that claim 14 (and dependent claims 15 and 17-20) is not *prima facie* obvious over Chaudhary in view of Wennemuth. Applicant thus considers that *prima facie* obviousness has not been established, and respectfully requests that this rejection be reconsidered and withdrawn.

B. Rejection of Claim 16 under 35 U.S.C. §103: Chaudhary + Wennemuth + Zimmermann

On pages 11-12 of the present Action, the Examiner rejects claim 16 under 35 USC 103(a) unpatentable over Chaudhary, Wennemuth and Zimmerman et al. ("Zimmermann"). Applicants respectfully traverse this rejection for the reasons already of record in addition to the observations set forth below:

The teachings of Chaudhary and Wennemuth are set forth above. Since Chaudhary, alone or in combination with Wennemuth, does not result in the subject-matter of the currently amended pending claims, in particular claim 14, Applicant submits that the Zimmerman approach does not rectify the defects of these disclosures such that the skilled person could apply the disclosed modes of administration (orally, parenterally, or topically; Office Action, page 11) of the PMCA inhibitor described by Chaudhary to the sperm cells discussed in Wennemuth to arrive at the subject-matter of claim 16 with a reasonable expectation of success.

Since *prima facie* obviousness has not been established for claim 16, Applicant respectfully requests that the present rejection under §103(a) be reconsidered and withdrawn.

C. Rejection of Claims 21-22 under 35 U.S.C. §103: Chaudhary + Wennemuth + Papurt

Claims 21-22 are rejected as being unpatentable over Chaudhary, Wennemuth and Papurt et al. ("Papurt") (Office Action, pages 13-14). Applicants respectfully traverse this rejection.

The teachings of Chaudhary and Wennemuth are set forth in detail above. As stated, neither of these publications provides the skilled person with a set of features, from a finite set of solutions, that offer both predictability and a reasonable expectation of success in achieving the claimed contraceptive methods without undue experimentation, especially considering the diversity of known PMCA isoforms, their localization, the variable response to PMCA inhibitors in a given cell type including sperm cells, and/or no well-defined role of the PMCA4 isoform on sperm mobility that could be useful as a basis for achieving the contraceptive solution in the manner of the presently claimed invention.

At least in view of the foregoing discussion, and for arguments already of record, Applicant considers that *prima facie* obviousness has not been established, and respectfully requests that this rejection be reconsidered and withdrawn.

D. CONCLUSION

In view of the amendment and arguments set forth above, Applicants consider that the objections and rejections in the Office Action mailed on June 10, 2010 have been overcome. Accordingly, we respectfully request that the Examiner issue a Notification of Allowance. It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement with or concession of that rejection, issue or comment.

In the event that the Examiner maintains any of the rejections under 35 USC §103, the Examiner is respectfully requested to restate the rejection, particularly in view of statements made herein seeking clarification and in view of the pending claims as presented and/or amended.

If the Examiner believes that a telephone conference would expedite the allowance of the present case, or has any questions or concerns regarding this Amendment, Applicants would welcome a telephone call to Applicant's undersigned attorney at the number indicated below.

Respectfully submitted,

Heimlich Law

Date: 09/10/2010

/Alan Heimlich/
Alan Heimlich / Reg 48808
Attorney for Applicant(s)
Customer No. 40418
Tel: 408 253-3860